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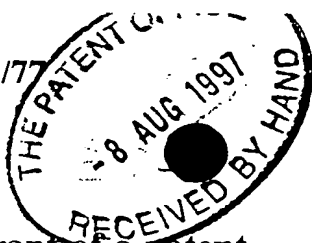
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Dated 21/8/1998.

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P01/7700 25.00 - 9716879.3

1/77

# Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office  
Cardiff Road  
Newport  
Gwent NP9 1RH

Your reference

28.66856

2. Patent application number  
(The Patent Office will fill in this part)

9716879.3

- 8 AUG 1997

3. Full name, address and postcode of the  
or of each applicant (*underline all surnames*)

Shire International Licensing BV  
Frederiksplein 42  
1017 XN  
Amsterdam  
The Netherlands

Patents ADP number (*if you know it*)

6964054001

If the applicant is a corporate body, give  
country/state of incorporation

The Netherlands

*Please see continuation sheet for details of co-applicant*

4. Title of the invention

Treatment of Attention Deficit  
Disorders

5. Name of your agent (*if you have one*)

Frank B. Dehn & Co.

"Address for service" in the United Kingdom  
to which all correspondence should be sent  
(*including the postcode*)

179 Queen Victoria Street  
London  
EC4V 4EL

Patents ADP number (*if you know it*)

166001

6. If you are declaring priority from one or more  
earlier patent applications, give the country  
and the date of filing of the or of each of these  
earlier applications and (*if you know it*) the or  
each application number

Country

Priority application number  
(*if you know it*)

Date of filing  
(*day / month / year*)

7. If this application is divided or otherwise  
derived from an earlier UK application,  
give the number and the filing date of  
the earlier application

Number of earlier application

Date of filing  
(*day / month / year*)

8. Is a statement of inventorship and of right  
to grant of a patent required in support of  
this request? (*Answer 'Yes' if:*

yes

- a) any applicant named in part 3 is not an inventor, or  
b) there is an inventor who is not named as an  
applicant, or  
c) any named applicant is a corporate body.  
See note (d))

# Patents Form 1/77

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Continuation sheets of this form

1

Description

11

Claim(s)

Abstract

Drawing(s)

10. If you are also filing any of the following, state how many against each item.

Priority documents

Translations of priority documents

Statement of inventorship and right to grant of a patent (*Patents Form 7/77*)

Request for preliminary examination and search (*Patents Form 9/77*)

Request for substantive examination (*Patents Form 10/77*)

Any other documents  
(please specify)

11.

I/We request the grant of a patent on the basis of this application.

*Frank Dehns*

Signature

Date 8 August 1997

12. Name and daytime telephone number of person to contact in the United Kingdom

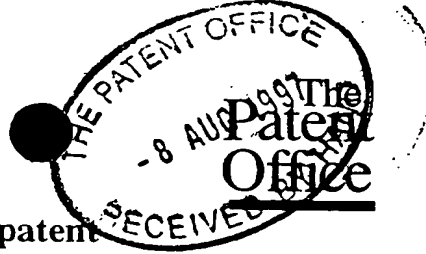
Anne R. Grant  
0171 206 0600

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Request for grant of a patent

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The Patent Office  
Cardiff Road  
Newport

Gwent NP9 1RH

1. Your reference 28.66856

2. Patent application number 9716879.3  
(The Patent Office will fill in this part) - 8 AUG 1997

3. Full name, address and postcode of the or of each applicant (underline all surnames)  
Ernir Snorrason  
Stigahlid 80  
105 Reykjavik  
Iceland

Patents ADP number (if you know it)

7266497001

If the applicant is a corporate body, give country/state of incorporation

4. Title of the invention Treatment of Attention Deficit Disorders

5. Name of your agent (if you have one) Frank B. Dehn & Co.

"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)

179 Queen Victoria Street  
London  
EC4V 4EL

Patents ADP number (if you know it) 166001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (if you know it) the or each application number

Country	Priority application number (if you know it)	Date of filing (day / month / year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing (day / month / year)

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer 'Yes' if:

yes

- a) any applicant named in part 3 is not an inventor, or
  - b) there is an inventor who is not named as an applicant, or
  - c) any named applicant is a corporate body.
- See note (d))

# Patents Form 1/77

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(please specify)

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0171 206 0600

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### Treatment of Attention Deficit Disorders

5       The present invention relates to a method of  
combatting attention deficit disorders (hereinafter  
referred to as ADD). In particular, the invention  
relates to the use of a pharmaceutically acceptable  
cholinesterase inhibitor in the manufacture of a  
10       medicament for use in combatting ADD.

          Attention deficit disorders affect children,  
adolescents and adults affecting up to 10% of children  
and at least 2% of adults. The childhood condition is  
often known as attention-deficit hyperactivity disorder  
15       (ADHD). Symptoms usually first manifest between the  
ages of 2 - 5. These children have a short attention  
span, motor hyperactivity, and are disorganised,  
forgetful and impulsive. ADHD can have a serious effect  
on the child's academic progress and performance and  
20       causes stress to family and teachers and difficulties in  
interacting with the child's peer group. The condition  
can persist into adult life. In adults, the major  
symptoms include distractibility, disorganisation and  
accident proneness. The condition in adults and  
25       children causes serious disruption to normal lifestyle  
patterns, and creates great stresses to all aspects of  
daily life, in the home, the workplace and in social  
situations. ADD as used herein covers both the adult  
and child forms of the condition, as well as  
30       hyperkinetic disorders and disorders which include any  
of the characterising criteria of the American  
Psychiatric Association's DSM-IV Classification of the  
disorders.

          Various therapies have been proposed but have not  
35       proved satisfactory, due *inter alia* to lack of efficacy  
and/or undesirable side effects. Stimulants such as  
dexamphetamine, methylphenidate and pemoline have been

used clinically in the management of ADD. Whilst they have been found to improve the primary manifestations such as motor activity, distractability and impulsivity in some sufferers, their side effects including anorexia, delayed onset of sleep, mood changes and exacerbation of pre-existing psychotic symptoms together with the possible potential for abuse, limits their utility. Other classes of drug such as tricyclic antidepressants have been suggested in the literature but are not generally regarded as being effective agents for the management of ADD. There is accordingly a need for a new therapeutic method for the management of ADD. The present invention provides such a method.

Thus we have surprisingly found that cholinesterase inhibitors such as galantamine can effectively combat ADD.

According to one aspect, the present invention provides a method of combatting ADD comprising administering to a subject a pharmaceutically acceptable cholinesterase inhibitor.

According to a related aspect, the invention provides the use of a pharmaceutically acceptable cholinesterase inhibitor in the manufacture of a medicament for combatting ADD.

As used herein the term 'combatting' includes both therapy and prophylaxis.

The invention encompasses the use of any cholinesterase inhibitor, provided of course that it is pharmaceutically acceptable.

Examples of cholinesterase inhibitors which may be used according to the invention include, but are not limited to, physostigmine, tacrine and tacrine analogues, fasciculin, metrifonate, heptyl-physostigmine, norpyridostigmine, norneostigmine, huperazine, donepezil and pro-drugs of any of these in which the inhibitor is modified in accordance with principles of pro-drug construction known in the art. Examples of such

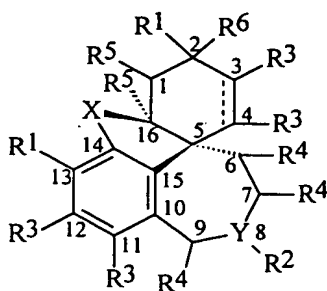


modifications include the introduction of hydrophilic or lipophilic groups to enhance solubility, or penetration through cell membranes, respectively.

Preferred cholinesterase inhibitors for use according to the invention are acetylcholinesterase inhibitors, particularly those which are capable of crossing the blood brain barrier.

Particularly preferred cholinesterase inhibitors for use according to the invention include galantamine, epigalantamine and norgalantamine, and analogues, salts and derivatives of any of these. Galantamine was previously known as galanthamine. It is a tertiary alkaloid which can be extracted from various snowdrop bulbs e.g. the Caucasian snowdrop *galanthus woronowii* (Amaryllidaceae) and related species and daffodil bulbs or made by chemical synthesis. It has a high selectivity for acetylcholinesterase as opposed to butyrylcholinesterase. It is active substantially selectively at nicotinic receptor sites with substantially little effect on muscarinic receptor sites.

Particularly preferred cholinesterase inhibitors for use in the invention are galantamine and its derivatives of formula (I):



I

wherein the broken line represents an optionally present double bond between carbon atoms 3 and 4, each R<sub>1</sub> is

independently selected from hydrogen, hydroxyl, straight or branched chain alkyl, hydroxyalkyl, carboxyalkyl amino, alkylamino, acyl, lower alkanoyl, cyano, sulfhydryl, C<sub>1-6</sub>alkoxy, alkylthio, aryloxy, arylthio, R<sub>3</sub>-substituted aryloxy, R<sub>3</sub>-substituted arylthio, aralkoxy, 5 an optionally R<sub>3</sub>-substituted aliphatic or aryl carbamyl group, aralkylthio, R<sub>3</sub>-substituted aralkoxy, R<sub>3</sub>-substituted aralkylthio, aryloxymethyl, R<sub>3</sub>-substituted aryloxymethyl, alkanoyloxy, hydroxy-substituted 10 alkanoyloxy, benzoyloxy, R<sub>3</sub>-substituted benzoyloxy, aryloxycarbonyl and R<sub>3</sub>-substituted aryloxycarbonyl,

R<sub>2</sub> is selected from hydrogen, straight or branched chain C<sub>1-6</sub>alkyl, alkenyl or alkaryl group, optionally substituted by a halogen atom or a cycloalkyl, hydroxy, 15 alkoxy, nitro, amino, aminoalkyl, acylamino, heteroaryl, heteroaryl-alkyl, aryl, arylalkyl, cyano, amyl, aroyl, cycloalkylmethyl, allyl, phenyl, R<sub>3</sub>-substituted phenyl, alkylphenyl, R<sub>3</sub>-substituted alkylphenyl, heterocyclyl selected from α- or β-furyl, α- or β-thienyl, thenyl, 20 pyridyl, pyrazinyl, and pyrimidyl, alkyl-heterocyclyl or R'-substituted heterocyclyl, where R' is alkyl or alkoxy,

each R<sub>3</sub> is independently selected from hydrogen, hydroxyl, sulfhydryl, alkyl, hydroxyalkyl, aryl, 25 aralkyl, alkoxy, mercaptoalkyl, aryloxy, thiaryloxy, alkaryloxy, mercaptoalkaryl, nitro, amino, N-alkylamino, N-arylamino, N-alkarylamino, fluoro, chloro, bromo, iodo, and trifluoromethyl,

each R<sub>4</sub> is independently selected from hydrogen, 30 halo, trifluoromethyl or C<sub>1-4</sub>-alkyl,

each R<sub>5</sub> is independently selected from hydrogen or hydroxymethyl,

R<sub>6</sub> is hydrogen or C<sub>1-6</sub>alkyl, or when R<sub>1</sub> at carbon atom 2 is hydroxyl, R<sub>6</sub> may be a moiety of formula I 35 wherein R<sub>6</sub> is hydrogen and R<sub>1</sub> is a linking bond; or

R<sub>1</sub> at carbon atom 2 and R<sub>6</sub> may jointly form semicarbazone,

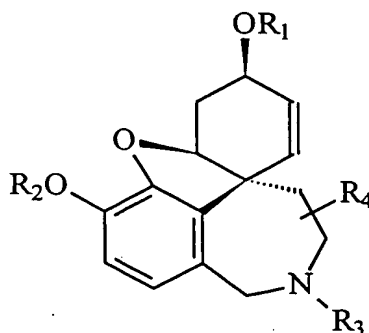
X is oxygen or  $\text{NR}_3$ ,

Y is nitrogen or phosphorus,

and methylenedioxy derivatives thereof and pharmaceutically acceptable acid addition salts thereof.

Of the compounds of formula I which may be used in the method of the invention, preferred compounds are those in which the alkyl moieties contain 1 to 8 carbon atoms, halogen atoms are preferably fluorine, bromine, chlorine, aryl moieties are preferably phenyl, cycloalkyl groups are preferably 3- to 7-membered rings, especially cyclopropyl or cyclobutyl, acyl groups are preferably lower alkanoyl groups and heteroaryl moieties are preferably 5- to 8-membered rings, e.g., thienyl, furyl, pyridyl, pyrrolyl, or pyrazinyl.

Preferred compounds of formula I are the compounds of formula II



II

wherein  $\text{R}^1$  and  $\text{R}^2$  which may be the same or different each represents a hydrogen atom or an acyl group, such as a lower alkanoyl group, e.g. an acetyl group or a straight-chained or branched alkyl group, e.g. methyl, ethyl, propyl, or isopropyl;

$\text{R}^3$  is a straight or branched chain alkyl, alkenyl or alkaryl group which is optionally substituted by a halogen atom or a cycloalkyl, hydroxy, alkoxy, nitro, amino, aminoalkyl, acylamino, heteroaryl, heteroarylalkyl, aroyl, aroylalkyl or cyano group; and

R<sup>4</sup> represents a hydrogen or a halogen atom attached to at least one of the ring carbons of the tetracyclic skeleton,

5 and pharmaceutically acceptable salts thereof, such as a hydrobromide, hydrochloride, methylsulphate or methiodide.

Formula II includes galantamine itself.

10 Particularly preferred is galantamine itself, and salts thereof such as halides for example galantamine hydrobromide and the use of these compounds in the manufacture of a medicament for combatting ADD provides a further aspect of the invention.

15 Among these compounds are those described in EP-A-236684 and WO88/08708, the disclosures of which are incorporated herein by reference. Galantamine and its derivatives of formula I and II may be prepared by the methods described in these publications.

20 The cholinesterase inhibitors for use in the invention include compounds which are functionally similar to galantamine. These are defined herein as compounds which possess an at least 10-fold selectivity, preferably an at least 20-fold selectivity, more preferably an at least 40-fold selectivity, and most preferably an at least 50 fold selectivity, for  
25 acetylcholinesterase as opposed to butyrylcholinesterase, when measured by the in vitro method of Thomsen and Kewitz: Selective Inhibition of Human Acetylcholinesterase by Galantamine in vitro and in vivo, Life Sciences, Vol 46, pp. 1553-1558 (1990), and  
30 T. Thomsen, H. Kewitz and O. Pleul, J. Clin. Chem. Clin. Biochem. 26 469-475 (1988). The in vitro test described by Thomsen and Kewitz in Life Sciences, Vol 46, pp 1553-1558 (1990) is the one referred to herein whenever  
35 numeric (10-fold, 20-fold, 40-fold) reference to selectivity for acetylcholinesterase as opposed to butyrylcholinesterase is made. According to Thomsen and Kewitz, galantamine hydrobromide, when tested under the

conditions described, shows a 50-fold selectivity; this selectivity value is taken as the "fix-point" whenever in vitro selectivities are discussed herein and could be used, for the purpose of determining the selectivities for other cholinesterase inhibitors, as a calibration value which is the one to establish with galantamine hydrobromide in any repetition of the experiment described by Thomsen and Kewitz. Thus, with reference to this determination method, a preferred acetylcholinesterase inhibitor is one which in the in vitro method described has an at least 10-fold selectivity for acetylcholinesterase as opposed to butyrylcholinesterase, such as an at least 20-fold selectivity for acetylcholinesterase as opposed to butyrylcholinesterase, e.g. an at least 40-fold selectivity for acetylcholinesterase as opposed to butyrylcholinesterase. A selectivity test is commercially available (from Sigma Diagnostics).

For use in the method of the invention the cholinesterase inhibitor such as galantamine and derivatives and salts thereof may be formulated according to conventional methods of pharmacy, together where appropriate with one or more pharmaceutically acceptable carriers, excipients or diluents such as, for example, are described in Remingtons Pharmaceutical Sciences. Such formulations may for example take the form of tablets, capsules, solutions, or lozenges, pessaries, creams, suppositories or transdermal formulations such as patches, creams, ointments or lotions, depending upon the administration route to be used, which may include enterally or parenterally, including orally or injection via the intravenous, intramuscular or subcutaneous routes, or intrathecally by means of an implanted device.

Oral and transdermal administration routes are preferred.

Precise dosage rates and regimes will depend upon

the individual patient and may be determined by the medical practitioner based on individual circumstances. For oral administration doses may be within the range of 5-100 mg per day, such as 2 to 70 mg per day eg. 10 to 30 mg. For transdermal administration galanthamine may be delivered in equivalent daily doses. For parenteral administration, dosages may be in the range of 0.1 to 100 mg per day, such as 5 to 100 mg per day, e.g. 10 to 50 mg per day, including 5 to 30 mg per day; lower dosages are often preferred.

Galantamine and its acid addition salts form crystals. They are generally only sparingly soluble in water at room temperature; therefore, injectable compositions are normally in the form of an aqueous suspension. If necessary, pharmaceutically-acceptable suspension aids may be employed. Typically, such a suspension will be employed at a concentration of 0.1-50 mg/ml, such as 1-50 mg/ml, more commonly 5-40 mg/ml, for example, 5-30 mg/ml or 10-40 mg/ml, such as 10-30 mg/ml, especially 20-30 mg/ml of galantamine.

Cholinesterase inhibitors such as galantamine and salts thereof may be used as the sole drug in the management of ADD, or may be used together with other agents useful in managing ADD.

The invention will now be described with reference to the following non-limiting examples.

#### Example 1

##### Formulation of tablets containing galantamine

##### Composition of 1 tablet containing 1 mg galantamine

Galantamine hydrobromide	0.001 g
Calcium phosphate	0.032 g
Lactose	0.005 g
Wheat Starch	0.0056 g
Microcrystalline Cellulose	0.015 g

Talc	0.0007 g
Magnesium Stearate	0.0007 g

Composition of 1 tablet containing 5 mg galantamine

5		
	Galantamine hydrobromide	0.005 g
	Calcium phosphate	0.024 g
	Lactose	0.004 g
	Wheat Starch	0.004 g
10	Microcrystalline Cellulose	0.04 g
	Talc	0.002 g
	Magnesium Stearate	0.001 g

Composition of 1 tablet containing 10 mg galantamine

15		
	Galantamine hydrobromide	0.010 g
	Lactose	0.040 g
	Wheat Starch	0.0234 g
	Microcrystalline Cellulose	0.0374 g
20	Talc	0.0036 g
	Magnesium Stearate	0.0012 g
	Gelatin	0.0044 g

Preparation

25 All the tablets are prepared according to routine  
tableting procedures.

Example 2

Treatment of patients suffering from ADD

30 Three patients aged 9 to 11 years diagnosed as  
having ADD were treated with 5 mg of galantamine given 3  
times per day for a total of 14 days. After this period  
of time, the patients showed marked improvement of  
symptoms, particularly as regards attention and  
35 restlessness, as judged on an ecological behavioural  
scale (translated: Barkley, RA et al, Assessing  
situational variation in children's problem behaviours:

The Home and School Situations Questionnaires, in RJ Prinz (Ed), Advances in Behavioural Assessment of Children and Families, vol 3, pp 157-176, Greenwich, CT, JAI Press, Inc).

5 A further cohort of two 5 year old patients with ADD have been treated and again symptoms have generally improved, especially attention, as measured by ANT (Amsterdam Neuropsychological Tests), which are standard tests that measure reaction times for different tasks.

10 The protocol in this case is first a baseline testing before medication and retesting after 2 days on medication and then after a week repeated testing. Ecological scales were also used before and are now being evaluated after one week after two weeks etc. for  
15 a treatment of one month duration. The following table shows a selection of results obtained for these two children before and after treatment with galantamine.

	Before:				After:			
	mean	Sd	miss <sup>1</sup>	Fa <sup>2</sup>	mean	Sd	miss	Fa
<b>Patient A</b>								
Baseline:	685	766			727	470		
GoNoGo	705	158	1	1	655	173	1	2
Sustained Att.	1302	565	14	13	1222	472	4	6
25 Focused Att.	1214	404			1352	434	0	
<b>Patient B</b>								
Baseline:	1051	899			780	418		
GoNoGo	804	162	2	9	766	172	3	3
30 Sustained Att.	1444	721	31	29	1152	600	20	50
Focused Att.	2444	1367	1		1166	270	3	

<sup>1</sup> Missed task

<sup>2</sup> Failed attempt

35 This data was normalized and submitted to error analysis that showed an improvement in attention (reduction in



time (msec) to complete certain tasks and with fewer errors) over 2.5 standard deviations after medication with galantamine hydrobromide 2.5 mg 3 times a day.

① 46 p23-18.

② 7 Aug 98.

③ Frank B Dehr Co.

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